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(72) Inventors: ROGER EDWARD FORD
PHILIP KNOWLES
EDWARD LUNT
STUART MALCOLM MARSHALL
ANTHONY JOHN HENTY SUMMERS

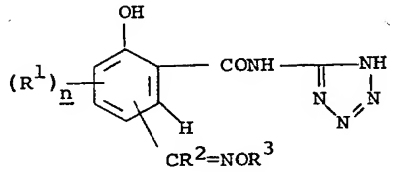
(19)

(54) N-(TETRAZOL-5-YL)-SALICYLAMIDE DERIVATIVES

(71) We, MAY & BAKER LIMITED, a British Company of Dagenham, Essex, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:-

This invention relates to new therapeutically useful benzamide derivatives, to processes for their preparation and to pharmaceutical compositions containing them.

As a result of research and experimentation, it has been found that the new benzamide derivatives of the general formula



I

[wherein R^1 represents a halogen (i.e. fluorine, chlorine, bromine or iodine) atom or a straight- or branched-chain alkyl, alkoxy, alkylthio, akylsulphonyl, alkylamino or alkylsulphamoyl group, each group containing from 1 to 6 carbon atoms, a dialkylsulphamoyl, dialkylamino, or dialkylcarbamoyl group (wherein the two alkyl groups may be the same or different and each contains from 1 to 4 carbon atoms), a straight- or branched-chain alkoxycarbonylamino, alkylcarbamoyl or alkanoylamino group containing from 2 to 6 carbon atoms, or a hydroxy, nitro, trifluoromethyl, aryl (e.g. phenyl), benzyloxycarbonylamino, amino, sulphamoyl, tetrazol-5-yl, carboxy, or carbamoyl group, and *n* represents zero or an integer 1 or 2, the substituents R^1 being the same or different when *n* represents 2, R^2 represents a hydrogen atom or a straight- or branched-chain alkyl group containing from 1 to 5 carbon atoms or an aryl (e.g. phenyl) group, and R^3 represents a hydrogen atom or a straight- or branched-chain alkyl group containing from 1 to 6 carbon atoms, optionally substituted by a phenyl group, or represents an aryl (e.g. phenyl) group optionally substituted by one or more substituents selected from halogen (i.e. fluorine, chlorine, bromine or iodine) atoms, straight- or branched-chain alkyl and alkoxy groups containing from 1 to 6 carbon atoms and hydroxy, trifluoromethyl and nitro groups], and pharmaceutically acceptable salts thereof, possess valuable pharmacological properties.

It will be understood by those skilled in the art that each of the hydrogen atoms depicted in general formula I in the moeities OH, CONH and NH may give rise to tautomerism and that all the resulting tautomeric forms may be present to a greater or lesser degree and are in a state of dynamic equilibrium with each other. Furthermore the substituents R^1, R^2 and R^3 may contain chiral centres, and thus give rise to optical isomerism, and the group

$-CR^2=NOR^3$ may be in the *syn* or *anti* configuration. The present invention embraces all optical and geometrical isomers of general formula I and all tautomers of compounds of general formula I, and mixtures thereof.

The present invention includes pharmaceutically acceptable salts of compounds of formula I with pharmaceutically acceptable bases. By the term "pharmaceutically acceptable salts" is meant salts the cations of which are relatively innocuous to the animal organism when used in therapeutic doses so that the beneficial pharmacological properties of the parent compounds of general formula I are not vitiated by side effects ascribable to those cations. Suitable salts include the alkali metal, e.g. sodium and potassium, and ammonium salts and salts of amines known in the art to be pharmaceutically acceptable, e.g. ethylenediamine, choline, diethanolamine, triethanolamine, octadecylamine, diethylamine, triethylamine, 2-amino-2-(hydroxymethyl)propane-1,3-diol and 1-(3,4-dihydroxyphenyl)-2-isopropylaminoethanol.

Pharmaceutically acceptable salts may be prepared by the reaction together of a compound of formula I and the appropriate base, for example at an elevated temperature, with or without an appropriate solvent, preferably followed by recrystallization from an appropriate solvent, for example a hydroxylic solvent, e.g. water, of the salt so formed.

In this specification when reference is made to compounds of formula I reference is also intended to their pharmaceutically acceptable salts, where the context so permits.

The benzene derivatives of the present invention possess valuable pharmacological properties, in particular properties of value in the treatment of respiratory disorders manifested by the interaction of tissue-fixed antibodies with specific antigens, such as allergic bronchial asthma.

Compounds within formula I as hereinbefore defined wherein $(R^1)_n$ represents an alkyl, preferably methyl or ethyl, group, R^2 represents a hydrogen atom or an alkyl, preferably methyl, group and R^3 represents a hydrogen atom or an alkyl group, preferably containing from 1 to 3 carbon atoms, e.g. a methyl or isopropyl group, or a phenyl or benzyl group, and their pharmaceutically acceptable salts, are of particular importance.

Compounds within formula I as hereinbefore defined wherein $(R^1)_n$ represents a substituent in the 5-position of the ring, and wherein the group $-CR^2=NOR^3$ is in the 3-position of the ring, are especially important.

Individual compounds of formula I of particular importance include the following:-

5-ethyl-2-hydroxy-3-[1-(hydroxyimino)ethyl]-*N*-(tetrazol-5-yl)-benzamide; A

5-ethyl-2-hydroxy-3-[1-(methoxyimino)ethyl]-*N*-(tetrazol-5-yl)-benzamide; B

5-ethyl-2-hydroxy-3-[1-(isopropoxyimino)ethyl]-*N*-(tetrazol-5-yl)-benzamide; C

3-[1-(benzyloxyimino)ethyl]-5-ethyl-2-hydroxy-*N*-(tetrazol-5-yl)-benzamide; D

2-hydroxy-3-[1-(hydroxyimino)ethyl]-5-methyl-*N*-(tetrazol-5-yl)-benzamide; E

2-hydroxy-3-[1-(methoxyimino)ethyl]-5-methyl-*N*-(tetrazol-5-yl)-benzamide; F

2-hydroxy-3-[1-(isopropoxyimino)ethyl]-5-methyl-*N*-(tetrazol-5-yl)-benzamide; G

5-ethyl-2-hydroxy-3-[1-(phenoxyimino)ethyl]-*N* (tetrazol-5-yl)benzamide; and H

2-hydroxy-3-(methoxyimino)methyl-5-methyl-*N*-(tetrazol-5-yl)-benzamide I:

and their pharmaceutically acceptable salts.

The letters of the alphabet A to I are assigned to the compounds for easy reference later in the specification, for example in the following Tables.

In pharmacological tests the compounds of formula I suppress the passive cutaneous anaphylactic (PCA) reaction resulting from combination of tissue-fixed reaginic antibodies with the appropriate antigenic material (termed reagin-allergen combination) and carried out in an essentially similar manner to that described by Ogilvie [Nature (Lond.), (1964), *204*, 91-92; Immunology, (1967), *12*, 112-131]. In the method used to test these compounds sera were obtained from rats which had been infected with larvae of the nematode parasite *Nippostrongylus brasiliensis*; as a result of the parasitic infestation reaginic antibodies are elaborated in the host mammal and are found in sera removed from such animals. Other, non-infected, rats received intradermal injections of appropriate dilutions of such sera and were then given the allergenic material along with Evans' blue dye intravenously forty-eight

hours later.

The allergenic material consisted of supernatant fluid after centrifugation of homogenates of adult *Nippostrongylus brasiliensis* worms which had been macerated in Tyrode's solution. The sites of PCA reactions were visualised by the effusion of Evan's blue dye from the circulation into those areas as a result of increased capillary permeability caused by the release of biologically-active substances from cells where reagin-allergen combination had occurred. The compounds of formula I when given intravenously to the rats just before injection of allergen, or administered orally thirty minutes before intravenous injection of allergen, were able to prevent the development of the PCA reaction, as shown below in Table I, Table II and Table III.

Table I shows the intravenous dose, expressed in mg/kg animal body weight, which produces 100% inhibition of the PCA reaction (ED_{100}).

Table II shows the percentage inhibition of the PCA reaction produced by an oral dose of 100 mg/kg animal body weight.

Table III shows the oral dose, expressed in mg/kg animal body weight, which produces 50% inhibition of the PCA reaction (ED_{50}).

TABLE I

Compound	A	B	C	D	E	F	G	H	I
ED_{100}	0.005	0.01	0.2	0.05	0.05	0.02	0.05	0.02	1

TABLE II

Compound	A	B	C	D	E	F	G
% inhibition	43	29	36	30	78	87	48

TABLE III

Compound	A	B	C	D	E	F	G	H	I
ED_{50}	100	0.3	0.48	0.59	1.0	3.2	0.77	0.83	6.3

The utility of the compounds of formula I is enhanced by the fact that they are only of very low toxicity to mammals, demonstrated by the following tests:-

Acute oral toxicity in mice

Mice were each treated orally with one of the compounds of formula I, and they were observed daily until there had been at least 3 consecutive days without any deaths. The LD_{50} figures obtained (doses lethal to 50% of mice tested) are shown below in Table IV, expressed in mg/kg animal body weight.

TABLE IV

Compound	A	B	C	D	F	G
LD_{50}	>1000	>1000	>1000	>1000	>1000	>1000

The symbol ">" means "greater than" in this specification. Where the LD_{50} is said to be ">1000", a more precise estimation of the LD_{50} was not possible because the number of deaths was too small, even at the highest dose used, 1000 mg/kg.

Acute intravenous toxicity in mice

Mice were each treated intravenously with an aqueous solution of the triethanolamine salt of one of the compounds of formula I, and they were observed until there had been at least 3 consecutive days without any deaths. The LD_{50} figures obtained (doses lethal to 50% of mice tested) are shown below in Table V, expressed in mg/kg animal body weight.

The aqueous solutions were prepared as follows:-

A mixture of the test compound and water was treated gradually with triethanolamine until complete solution occurred. The solution was then diluted with water to a concentration of either 1% w/v or 2% w/v.

Various volumes of these solutions were then administered to the mice.

TABLE V

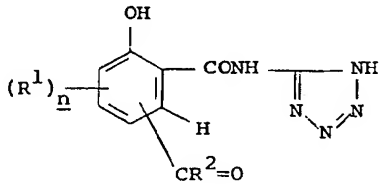
Compound	A	B	C	D	E	F	G
Concentration of test solution (% w/v)	1 or 2 *	1 or 2 *	1	1	2	2	2
LD_{50}	300	240	140	140	410	320	168

*For lower doses 1% w/v solution was used, and for higher doses 2% w/v solution was used.

Compounds of formula I may be prepared by the application or adaptation of known methods.

By the term "known methods", as used in this specification, is meant methods heretofore used or described in the literature.

Thus, according to a feature of the present invention, compounds of formula I are prepared from compounds of the general formula:-



II

(wherein R^1, R^2 and n are as hereinbefore defined) by the application or adaptation of known methods for the preparation of oximes from aldehydes and ketones, for example by reaction with compounds of the general formula:-

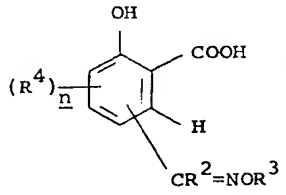
H_2NOR^3 III

(wherein R^3 is as hereinbefore defined) in the form of a salt, e.g. the hydrochloride, thereof.

Generally the reaction is carried out in the presence of a base, for example the hydroxide, carbonate or bicarbonate of an alkali metal, e.g. sodium hydroxide, sodium carbonate, or sodium bicarbonate, in a polar medium such as *N*-methylpyrrolidone, and at a temperature near or above the ambient temperature, e.g. 15-100°C.

Compounds of general formula II are described and claimed in our copending Application No. 46174/76. (Serial No. 1561350).

According to a further feature of the present invention, compounds of formula I (except those wherein R^1 represents an alkylamino, amino or carboxy group) are prepared by the reaction of 5-aminotetrazole with carboxylic acids of the general formula:-



IV

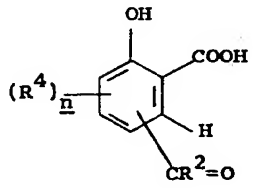
[wherein R^4 represents a halogen (i.e. fluorine, chlorine, bromine or iodine) atom or a straight- or branched-chain alkyl, alkoxy, alkylthio, alkylsulphonyl, or alkylsulphamoyl group containing from 1 to 6 carbon atoms, a dialkylsulphamoyl, dialkylamino, or dialkylcarbamoyl group (wherein the two alkyl groups may be the same or different and each contains from 1 to 4 carbon atoms), a straight- or branched-chain alkoxycarbonylamino, alkylcarbamoyl, or alkanoylamino group containing from 2 to 6 carbon atoms, or a hydroxy, nitro, trifluoromethyl, aryl (e.g. phenyl), benzyloxycarbonylamino, sulphamoyl, tetrazol-5-yl or carbamoyl group, and n represents zero or an integer 1 or 2, the substituents R^4 being the same or different when n represents 2, and R^2 and R^3 are as hereinbefore defined].

The reaction between 5-aminotetrazole and carboxylic acids of formula IV may be carried out in the presence of a condensation agent such as dicyclohexylcarbodiimide in the

presence of a solvent such as pyridine.

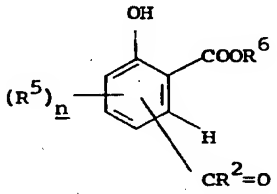
The aldehydes and ketones of formula II may be prepared by the application or adaptation of known methods.

For example, compounds of formula II (except those wherein R^1 represents an alkylamino, amino or carboxy group) may be prepared by the reaction of 5-aminotetrazole with carboxylic acids of the general formula:-



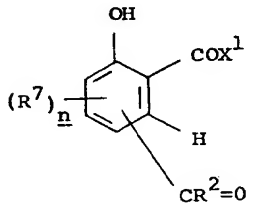
V

[wherein R^4, n and R^2 are as hereinbefore defined], or (except when R^1 represents an alkylamino, amino or carboxy group) with esters thereof of the general formula:-



VI

[wherein R^5 is as defined for R^4, R^6 represents a straight- or branched-chain alkyl group containing from 1 to 4 carbon atoms, and R^2 is as hereinbefore defined) or (except when R^1 represents an alkylamino, alkoxycarbonylamino, alkanoylamino, hydroxy, benzyloxycarbonylamino, amino, carboxy or carbamoyl group) with acid halides thereof of the general formula:-



VII

[wherein R^7 represents a halogen (i.e. fluorine, chlorine, bromine or iodine) atom or a straight- or branched-chain alkyl, alkoxy, alkylthio, alkylsulphonyl or alkylsulphamoyl group containing from 1 to 6 carbom atoms, a dialkylsulphamoyl, dialkylamino, or dialkylcarbamoyl group (wherein the two alkyl groups may be the same or different and each contains from 1 to 4 carbon atoms), a straight- or branched-chain alkyl-carbamoyl group containing from 2 to 6 carbon atoms, or a nitro, trifluoromethyl, aryl (e.g. phenyl), sulphamoyl, or tetrazol-5-yl group, and n represents zero or an integer 1 or 2, the substituents R^7 being the same or different when n represents 2, X^1 represents a chlorine or bromine atom and R^2 is as hereinbefore defined].

The reaction between 5-aminotetrazole and carboxylic acids of formula V may be carried out in the presence of a condensation agent such as dicyclohexylcarbodiimide in the presence of a solvent such a pyridine, or (except when R^4 represents an alkanoylamino, alkoxycarbonylamino, hydroxy, benzyloxycarbonylamino or carbamoyl group) phosphorus trichloride, preferably in the presence of an inert solvent such as benzene, toluene or xylene, preferably in dry conditions, at temperatures between, for example, 10°C. and 100°C.

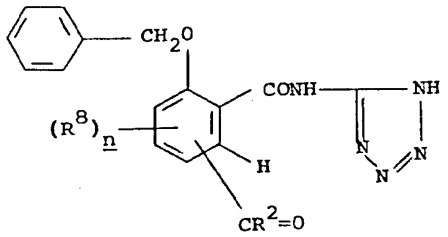
The reaction between 5-aminotetrazole and esters of formula VI may be carried out with or without a solvent, for example alkanols containing up to 4 carbon atoms, (e.g. methanol), aromatic solvents (e.g. xylene) or dimethylformamide, preferably at elevated temperatures and optionally in the presence of an alkali metal alkoxide containing from 1 to 4 carbon atoms.

Esters of formula VI may be prepared from the corresponding carboxylic acids of

formula V by the application or adaptation of known methods for the esterification of 2-carboxyphenols such as salicylic acid.

The reaction between acid halides of formula VII (which may be prepared from the corresponding carboxylic acids within formula V by the application or adaptation of known methods, for example by reaction with thionyl chloride, phosphorus trichloride or oxalyl chloride, optionally *in situ*) and 5-aminotetrazole may be carried out preferably in an inert solvent, for example benzene, toluene, xylene or pyridine, preferably at elevated temperatures, for example the reflux temperature of the reaction mixture.

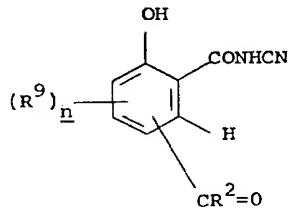
As an alternative, compounds of formula II (except those wherein R^1 represents an alkylthio, nitro or benzyloxycarbonylamino group) may be prepared by reduction of compounds of the general formula:-



VIII

[wherein R^8 represents a halogen (i.e. fluorine, chlorine, bromine or iodine) atom or a straight- or branched-chain alkyl, alkoxy, alkylsulphonyl, alkylamino or alkylsulphamoyl group containing from 1 to 6 carbon atoms, a dialkylsulphamoyl, dialkylamino, or dialkylcarbamoyl group (wherein the two alkyl groups may be the same or different and each contains from 1 to 4 carbon atoms), a straight- or branched-chain alkoxycarbonylamino, alkylcarbamoyl or alkanoylamino group containing from 2 to 6 carbon atoms, or a hydroxy, trifluoromethyl, aryl (e.g. phenyl), amino, sulphamoyl, tetrazol-5-yl, carboxy or carbamoyl group, and *n* represents zero or an integer 1 or 2, the substituents R^8 being the same or different when *n* represents 2, and R^2 is as hereinbefore defined]. Generally reduction is carried out by hydrogenation in the presence of a catalyst such as palladium on charcoal in an organic solvent, for example *N*-methylpyrrolid-2-one or ethanol.

As a further alternative, compounds of formula II (except those wherein R^1 represents an alkylamino, alkoxy-carbonylamino, alkanoylamino, hydroxy, benzyloxycarbonylamino, amino, carboxy or carbamoyl group) may be prepared by the reaction of compounds of the general formula:-



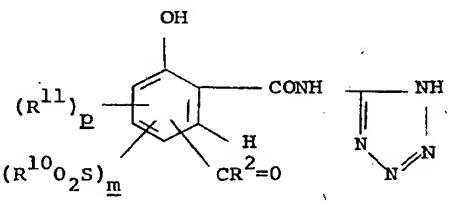
IX

[wherein R^9 represents a halogen (i.e. fluorine, chlorine, bromine or iodine) atom or a straight- or branched-chain akyl, alkoxy, alkylthio, alkylsulphonyl or alkylsulphamoyl group containing from 1 to 6 carbon atoms, a dialkylsulphamoyl, dialkylamino, or dialkylcarbamoyl group (wherein the two alkyl groups may be the same or different and each contains from 1 to 4 carbon atoms), a straight- or branched-chain alkyl-carbamoyl group containing from 2 to 6 carbon atoms, or a nitro, trifluoromethyl, aryl (e.g. phenyl), sulphamoyl, or tetrazol-5-yl group, and *n* represents zero or an integer 1 or 2, the substituents R^9 being the same or different when *n* represents 2, and R^2 is as hereinbefore defined] with hydrazoic acid or a salt thereof, for example sodium azide, potassium azide or ammonium azide.

Generally the reaction is carried out in an organic solvent, e.g. *N*-methylpyrrolid-2-one, preferably at a temperature between 0°C. and 120°C.

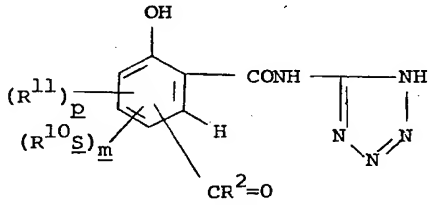
Compounds of formula IX may be prepared by reaction of compounds of formula VII with cyanamide. Preferably the reaction is carried out in an inert solvent, in the presence of an acid-binding agent, for example pyridine, which may also serve as reaction medium.

As a further alternative, compounds of the general formula:-



X

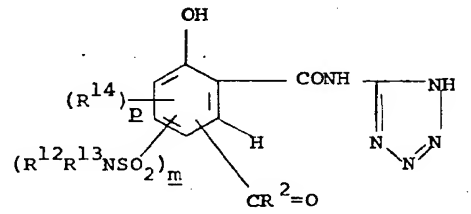
[wherein R^{10} represents a straight- or branched- chain alkyl group containing from 1 to 6 carbon atoms, *m* represents an integer 1 or 2, R^{11} represents a halogen, (i.e. fluorine, chlorine, bromine or iodine) atom or a straight- or branched-chain alkyl, alkoxy, alkylsulphonyl, or alkylsulphamoyl group containing from 1 to 6 carbon atoms, a dialkylsulphamoyl or dialkylcarbamoyl group (wherein the two alkyl groups may be the same or different and each contains from 1 to 4 carbon atoms), a straight- or branched-chain alkoxycarbonylamino, alkylcarbamoyl or alkanoylamino group containing from 2 to 6 carbon atoms, or a nitro, trifluoromethyl, aryl (e.g. phenyl), benzyloxycarbonylamino, sulphamoyl, tetrazol-5-yl, carboxy or carbamoyl group, and *p* represents zero or one, or R^{11} represents a hydroxy group in the *para*-position relative to the tetrazolylcarbamoyl group, and the sum of *m* and *p* is 1 or 2, and R^2 is as hereinbefore defined] within general formula II are prepared by the oxidation of compounds of the general formula:-



XI

(wherein R^2, R^{10}, R^{11}, *m* and *p* are as hereinbefore defined). The reaction may be carried out by the action of a peroxy acid, for example *m*-chloroperbenzoic acid, in an inert solvent, e.g. sulpholane, or alternatively by the action of aqueous hydrogen peroxide solution, preferably in the presence of a carboxylic acid (e.g. acetic acid) and optionally at an elevated temperature.

As a further alternative, compounds of the general formula:-

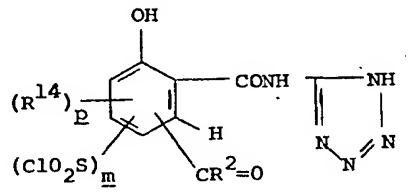


XII

[wherein R^{12} and R^{13} may be the same or different and each represents a hydrogen atom or a straight- or branched-chain alkyl group containing from 1 to 4 carbon atoms, R^{14} represents a halogen (i.e. fluorine, chlorine, bromine or iodine) atom or a straight- or branched-chain alkyl, alkoxy, alkylthio or alkylsulphonyl group containing from 1 to 6 carbon atoms or a dialkylamino group (wherein the two alkyl groups may be the same or different and each contains from 1 to 4 carbon atoms) or a hydroxy, nitro, trifluoromethyl, aryl (e.g. phenyl), tetrazol-5-yl or carboxy group, *m* represents an integer 1 or 2, *p* represents zero or one, and the sum of *m* and *p* is 1 or 2, and R^2 is as hereinbefore defined] within general formula II are prepared by the action of amines of the general formula:-

$$HNR^{12}R^{13} \qquad \text{XIII}$$

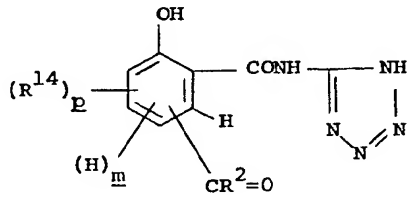
(wherein R^{12} and R^{13} are as hereinbefore defined) on compounds of the general formula:-



XIV

(wherein R^2, R^{14}, *m* and *p* are as hereinbefore defined). The reaction may be carried out in an organic solvent (e.g. ethanol) at ambient or elevated temperatures.

Compounds of formula XIV may be prepared by the action of chlorosulphonic acid on compounds of the general formula:-

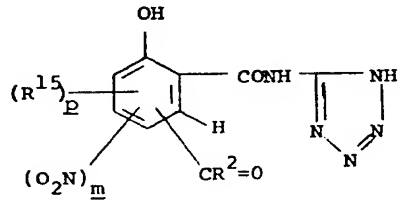


XV

(wherein R^2, R^{14}, *m* and *p* are as hereinbefore defined).

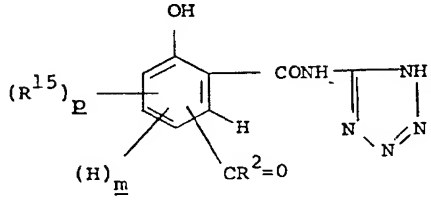
As will be apparent to those skilled in the art, the position or positions of the group or groups $-(SO_2R^{12}R^{13})m$ which may be introduced in this manner depends upon the nature and position of the group or groups $-(R^{14})_p$ and upon the reaction conditions employed in converting compounds of formula XV to compounds of formula XIV, and may be determined by a minimum amount of experimentation.

As a further alternative, compounds of the general formula:-



XVI

[wherein R^{15} represents a halogen (i.e. fluorine, chlorine, bromine or iodine) atom or a straight- or branched-chain alkyl, alkoxy, alkylsulphonyl, alkylamino or alkylsulphamoyl group containing from 1 to 6 carbon atoms, a dialkylsulphamoyl, dialkylamino, or dialkylcarbamoyl group (wherein the two alkyl groups may be the same or different and each contains from 1 to 4 carbon atoms), a straight- or branched-chain alkoxycarbonylamino, alkylcarbamoyl or alkanoylamino group contaning from 2 to 6 carbon atoms, or a hydroxy, nitro, trifluoromethyl, amino, sulphamoyl, tetrazol-5-yl, carboxy or carbamoyl group, and *p* represents zero or one, *m* represents 1 or 2, and the sum of *m* and *p* is 1 or 2, and R^2 is as hereinbefore defined] within general formula II are prepared by the nitration of compounds of the general formula:-

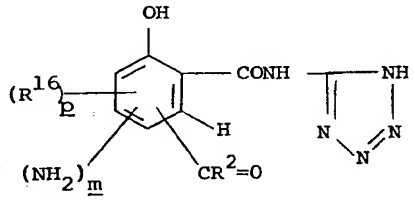


XVII

(wherein R^2, R^{15}, *m* and *p* are as hereinbefore defined) by the application or adaptation of known methods for the nitration of phenyl moieties, for example by the action of a mixture of concentrated nitric acid and concentrated sulphuric acid.

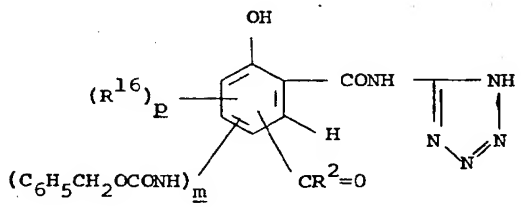
As will be apparent to those skilled in the art, the position or positions of the nitro group or groups which may be introduced in this manner depends upon the nature and position of the group or groups $-(R^{15})_p$ and upon the reaction conditions employed in the nitration, and may be determined with a minimum amount of experimentation.

According to a further alternative, compounds of general formula:-



XVIII

[wherein R^{16} represents a halogen (i.e. fluorine, chlorine, bromine or iodine) atom or a straight- or branched-chain alkyl, alkoxy, alkylthio, alkylsulphonyl, alkylamino or alkylsulphamoyl group containing from 1 to 6 carbon atoms, a dialkyl-sulphamoyl, dialkylamino, or dialkylcarbamoyl group (wherein the two alkyl groups may be the same or different and each contains from 1 to 4 carbon atoms), a straight- or branched-chain alkylcarbamoyl or alkanoylamino group containing from 2 to 6 carbon atoms, or a hydroxy, nitro, trifluoromethyl, aryl (e.g. phenyl), sulphamoyl, tetrazol-5-yl, carboxy, or carbamoyl group, p represents zero or one, m represents 1 or 2 and the sum of m and p is 1 or 2, and R^2 is as hereinbefore defined] within general formula II are prepared by the reaction of compounds of the general formula:-



XIX

(wherein R^2, R^{16}, m and p are as hereinbefore defined) within general formula II, with acetic acid and hydrogen bromide.

Compounds of formula IV may be prepared, for example, from compounds of formula V by the application or adaptation of the methods hereinbefore described for the preparation of compounds of formula I from compounds of formula II, for example, especially when R^3 represents an alkyl group of 1 to 3 carbon atoms, the aforementioned polar medium may be an aqueous alkanol, e.g. the corresponding alkanol of the general formula:-

$$R^{17}OH \qquad XX$$

wherein R^{17} represents an alkyl group of 1 to 3 carbon atoms.

The following Examples illustrate the preparation of the new compounds of the present invention.

The Reference Examples following thereafter illustrate the preparation of starting materials used in the Examples.

EXAMPLE 1

Compounds, A, B, C, D, E, F, and G

Hydroxylamine hydrochloride (2.8 g.) and anhydrous sodium carbonate (1.6 g.) were suspended together in *N*-methyl-pyrrolidone (40 ml.) and the mixture was heated at 80°C. for 10 minutes. 3-Acetyl-5-ethyl-2-hydroxy-*N*-(tetrazol-5-yl)-benzamide (5.5 g.) was then added to the mixture, and the mixture was stirred at 80°C. for 15 hours. The mixture was poured into water (300 ml.) and the resulting mixture was acidified by treatment with concentrated hydrochloric acid. The precipitated solid was filtered off and recrystallised from aqueous dimethylformamide, to give 5-ethyl-2-hydroxy-3-[1-(hydroxyimino)ethyl]-*N*-(tetrazol-5-yl)benzamide (3.9 g.), m.p. 249-250°C. (with decomposition).

By proceeding in a similar manner, but replacing the hydroxylamine hydrochloride, used

as a starting material, by the appropriate quantities of:-
O-methylhydroxylamine hydrochloride;
O-isopropylhydroxylamine hydrochloride; and
O-benzylhydroxylamine hydrochloride; there were prepared:-
5-ethyl-2-hydroxy-3-[1-(methoxyimino)etyl]-*N*-(tetrazol-5-yl)-benzamide, m.p. 272-275°C. (with decomposition);
5-ethyl-2-hydroxy-3-[1-(isopropoxyimino)ethyl]-*N*-(tetrazol-5-yl)-benzamide, m.p. 239-240°C. (with decomposition) (recrystallised from 2-ethoxyethanol); and
3-[1-(benzyloxyimino)ethyl]-5-ethyl-2-hydroxy-*N*-(tetrazol-5-yl)-benzamide, m.p. 233-235°C. (recrystallised from ethanol); respectively.

By again proceeding in a similar manner, but replacing the 3-acetyl-5-ethyl-2-hydroxy-*N*-(tetrazol-5-yl)-benzamide, used as a starting material, by the appropriate quantity of 3-acetyl-2-hydroxy-5-methyl-*N*-(tetrazol-5-yl)-benzamide, there was prepared 2-hydroxy-3-[1-(hydroxyimino)-ethyl]-5-methyl-*N*-(tetrazol-5-yl)benzamide, m.p. 253-254°C. (with decomposition) (recrystallised from a mixture of dimethylformamide and acetic acid).

By again proceeding in a similar manner, using 3-acetyl-2-hydroxy-5-methyl-*N*-(tetrazol-5-yl)benzamide as a starting material and replacing the hydroxylamine hydrochloride, used as a starting material, by the appropriate quantities of *O*-methylhydroxylamine hydrochloride, and *O*-isopropylhydroxylamine hydrochloride, respectively, there were prepared:-
2-hydroxy-3-[1-(methoxyimino)ethyl]-5-methyl-*N*-(tetrazol-5-yl)-benzamide, m.p, 283-285°C. (with decomposition); and
2-hydroxy-3-[1-(isopropoxyimino)ethyl]-5-methyl-*N*-(tetrazol-5-yl)benzamide, m.p. 244-245°C. (with decomposition) (recrystallised from 2-ethoxyethanol).

EXAMPLE 2

Compound H

By proceeding in a manner similar to that hereinbefore described in Example 1, but replacing the hydroxylamine hydrochloride used as a starting material by the appropriate quantity of *O*-phenylhydroxylamine hydrochloride, there was prepared 5-ethyl-2-hydroxy-3-[1-(phenoxyimino)ethyl]-*N*-(tetrazol-5-yl)benzamide, m.p. 265-270°C. (with decomposition) (recrystallised from 90% w/w formic acid).

EXAMPLE 3

Compound I

A stirred solution of 3-(methoxyiminomethyl)-5-methylsalicylic acid (2.09 g.) in dry pyridine (25 ml.) was treated with anhydrous 5-aminotetrazole (0.24 g.), followed by dicyclohexylcarbodiimide (2.27 g.), and the resulting suspension was stirred at room temperature overnight.

The mixture was then evaporated to dryness and the residue was stirred with a mixture of concentrated aqueous ammonia solution (e.g. 0.880; 25 ml.) and dilute aqueous ammonia solution (2N; 25 ml.) for 1 hour. The mixture was then filtered and the filtrate was acidified to pH 1 by treatment with concentrated hydrochloric acid. The resulting yellow solid (1.8 g.) was filtered off and recrystallised from aqueous dimethylformamide, to give 2-hydroxy-3-methoxyimino)methyl-5-methyl-*N*-(tetrazol-5-yl)benzamide (0.6 g.), m.p. 275-276°C. (with decomposition).

Reference Example 1

Purified thionyl chloride (3 ml.) was added to a suspension of dried 3-acetyl-5-methylsalicylic acid (1.94 g.) in dry benzene (30 ml.) and the mixture was stirred and heated at reflux for 90 minutes. The resulting clear solution was evaporated *in vacuo* at below 40°C.

The residual oil was treated with dry benzene and again evaporated *in vacuo* and this procedure was repeated several times to remove the remaining thionyl chloride.

The 3-acetyl-5-methylsalicyloyl chloride thus obtained was dissolved in dry benzene (30 ml.) and treated with anhydrous 5-aminotetrazole (1.7 g.) and the mixture was stirred and heated at reflux for 15 hours. The mixture was then allowed to cool and was treated with petroleum ether (b.p. 40-60°C; 30 ml.). The resulting solid was filtered off, washed with petroleum ether (b.p. 40-60°C.) and stirred with hydrochloric acid (2N; 30 ml.). The undissolved solid was filtered off, washed with hydrochloric acid (2N) and with water, and was then dried and recrystallised twice from a mixture of dimethylformamide and acetic acid to give 3-acetyl-2-hydroxy-5-methyl-*N*-(tetrazol-5-yl)benzamide, m.p. 280-282°C. (with decomposition).

Reference Example 2

A mixture of 3-acetyl-5-ethylsalicylic acid (55.0 g.) and dicyclohexylcarbodiimide (60.1 g.)

in dry pyridine (550 ml.) was stirred at 25°C. for one hour. Anhydrous 5-aminotetrazole (2.47 g.) was then added to the mixture, and stirring was continued at 60°C. for 24 hours. The pyridine was removed *in vacuo*, and the residue was treated with aqueous ammonia solution (2N; 500 ml.). The resulting slurry was stirred at between 90° and 100°C. for 15 minutes. The insoluble dicyclohexylurea was filtered off, and the filtrate was acidified by treatment with concentrated hydrochloric acid. The resulting green precipitate was filtered off and recrystallised twice from aqueous dimethylformamide to give 3-acetyl-5-ethyl-2-hydroxy-*N*-(tetrazol-5-yl)benzamide (35.4 g.) in the form of a pale yellow solid, m.p. 257-258°C. (with decomposition).

Reference Example 3

By the application or adaptation of the methods described by Amin *et al*, J. Indian Chem. Soc., 1964, *41*, 833, to 2-acetoxy-5-methylbenzoic acid, there was prepared 3-acetyl-5-methylsalicylic acid, m.p. 132-134°C.

Reference Example 4

By the application of the method of Bumgardner and Lilly, Chemistry and Industry, (1962), 559, to hydroxylamine-*O*-sulphonic acid (42.5 g.), there was prepared *O*-phenylhydroxylamine, which was dissolved in methylcyclohexane and treated with a saturated solution of hydrogen chloride in ethanol, to give *O*-phenylhydroxylamine hydrochloride (4.3 g.) m.p. 131°C. (with decomposition).

Reference Example 5

Methoxylamine hydrochloride (10.02 g.) was treated with a solution of sodium hydroxide (3.6 g.) in water (50 ml.), followed by a solution of 3-formyl-5-methylsalicylic acid (5.4 g.) in methanol (70 ml.), at room temperature and with stirring. The mixture was heated at 50°C. for 20 hours and was then concentrated *in vacuo* to about half its original volume, and was acidified to pH 1 by treatment with concentrated hydrochloric acid. The resulting white solid was filtered off, washed with water and recrystallised from aqueous methanol, to give 3-(methoxyiminomethyl)-5-methylsalicylic acid (4.45 g.), m.p. 161-164°C., sufficiently pure for use in Example 3 above.

Reference Example 6

5-Methylsalicylic acid (30 g.) was treated according to the general method described in United States Patent Specification No. 3,833,660, to give 3-formyl-5-methylsalicylic acid (19.0 g.) m.p. 190-194°C. (recrystallised from aqueous ethanol).

The present invention includes within its scope pharmaceutical compositions which comprise one or more compounds of formula I together with a pharmaceutical carrier or coating. In clinical practice the compounds of the present invention will normally be administered orally, sub-lingually, nasally, rectally or parenterally.

Solid compositions for oral administration include compressed tablets, pills, dispersible powders, and granules. In such solid compositions the active compound or compounds is or are mixed with at least one inert diluent such as calcium carbonate, potato starch, alginic acid, or lactose. The compositions may also comprise, as is normal practice, additional substances other than inert diluents, e.g. lubricating agents, such as magnesium stearate. Liquid compositions for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, and elixirs containing inert diluents commonly used in the art, such as water and liquid paraffin. Besides inert diluents such compositions may also comprise adjuvants, such as wetting and suspending agents, and sweetening, flavouring, perfuming and preserving agents. The compositions according to the invention, for oral administration, also include capsules of absorbable material such as gelatin containing the active compound or compounds with or without the addition of diluents or excipients.

The compound(s) may also be administered sublingually by administration of relatively slowly dissolving tablets which, besides including inert diluents as commonly used in the art, may contain sweetening, flavouring, perfuming and preserving agents.

Solid compositions for rectal administration include suppositories formulated in manner known *per se* and containing the active compound or compounds.

Preparations according to the invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, or emulsions. Examples of non-aqueous solvents or suspending media are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. These compositions may also contain adjuvants such as preserving, wetting, emulsifying and dispersing agents. They may be sterilised, for example, by filtration through a bacteria-retaining filter, by incorporation of sterilising agents in the compositions, by irradiation, or by heating. They may also be manufactured in the form of sterile solid compositions which can be dissolved in sterile

water or some other sterile injectable medium immediately before use.

The percentage of active ingredient in the compositions of the invention may be varied, it being necessary that it should constitute a proportion such that a suitable dosage for the therapeutic effect desired shall be obtained. Obviously several unit dosage forms may be administered at about the same time. Generally the compositions should contain 0.1% to 50% by weight of benzamide derivative especially when in tablet form. When in aerosol form as hereinafter described the compositions should contain 0.2 to 5%, preferably 2 to 5%, by weight of benzamide derivative.

The active compound or compounds may also be administered by methods known for the inhalation of drugs which are not themselves gaseous under normal conditions of administration. Thus, a solution of the compound or compounds in a suitable pharmaceutically acceptable solvent, for example water, can be nebulized by a mechanical nebulizer, for example a Wright Nebulizer (a registered Trade Mark), to give an aerosol of finely-divided liquid particles suitable for administration for inhalation orally or nasally. The solutions may contain stabilizing agents and buffering agents to give an isotonic character, e.g. sodium chloride, sodium citrate and citric acid.

Means for producing self-propelling compositions for generating aerosols for the administration of medicaments are, for example, described in detail in United States Patent Specifications Nos. 2,868,691 and 3,095,355.

The compounds or compounds may also be administered orally by inhalation in the form of a dry micronised powder, which may be diluted with one or more suitable pharmaceutically acceptable inert solid diluents selected from, for example, lycopodium, boric acid, starch, bismuth subcarbonate and heavy magnesium carbonate.

The pharmaceutical compositions of the present invention may contain, in addition to the compound or compounds of formula I, one or more substances known *per se* to have bronchodilating actions in man, for example, isoprenaline, salbutamol and prostaglandin E_1 (PGE_1).

It is highly desirable that the aerosols or micronised powders should have a particle size less than about 10 microns and preferably less than 5 microns, for example, between 0.5 and 3 microns, to ensure effective distribution to very narrow bronchioles. Preferably, administration is by means of devices enabling controlled quantities of the active ingredients to be administered, for example by means of metered valves.

The dose of the compounds of general formula I employed depends upon the desired therapeutic effect, the route of administration and the duration of the treatment. In the adult, the doses are generally between 0.002 and 4, preferably between 0.002 and 0.4 mg/kg body weight per day by administration by inhalation in divided doses, and generally between 0.4 and 2000, preferably between 0.4 and 40 mg./kg. body weight per day by oral administration.

The following Composition Examples illustrate pharmaceutical compositions according to the present invention:-

Composition Example 1

Micromilled 5-ethyl-2-hydroxy-3-[1-(methoxyimino)-ethyl]-*N*-(tetrazol-5-yl)benzamide, (600 mg.) and emulsifier YN (150 mg; a mixture of ammonium compounds of phosphatidic acids derived from rape seed oil) were placed in an aluminium vial (20 ml. capacity). Trichloromonofluoromethane (2.7 g.), dichlorodifluoromethane (9.4 g.) and dichlorotetrafluoroethane (4.4 g.) were then added, to give a total volume of 12.5 ml. The vial was sealed with a metered valve delivering a dose of 0.05 ml. Each dose (generated from 0.05 ml. of suspension) of aerosol released from the pressurized pack thus obtained contained 2.4 mg. of 5-ethyl-2-hydroxy-3-[1-(methoxyimino)-ethyl]-N-(tetrazol-5-yl)benzamide.

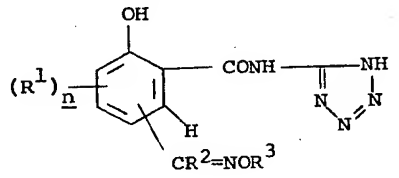
Composition Example 2

Capsules for oral administration were made up in the usual manner by filling no. 2 size gelatine capsules each with 255 mg. of the following composition:-

5-ethyl-2-hydroxy-3-[1-(methoxyimino)-ethyl]-*N*-(tetrazol-5-yl)benzamide.	150 mg.
lactose	50 mg.
starch	50 mg.
magnesium stearate	2.5 mg.
Aerosil (a registered Trade Mark)	2.5 mg.

WHAT WE CLAIM IS:-

1. Benzamide derivatives of the general formula:-



I

[wherein R^1 represents a halogen atom or a straight- or branched-chain alkyl, alkoxy, alkylthio, alkylsulphonyl, alkylamino or alkylsulphamoyl group, each such group containing from 1 to 6 carbon atoms, a dialkylsulphamoyl, dialkylamino, or dialkylcarbamoyl group (wherein the two alkyl groups may be the same or different and each contains from 1 to 4 carbon atoms), a straight- or branched-chain alkoxycarbonylamino, alkylcarbamoyl or alkanoylamino group containing from 2 to 6 carbon atoms, or a hydroxy, nitro, trifluoromethyl, aryl, benzyloxycarbonylamino, amino, sulphamoyl, tetrazol-5-yl, carboxy or carbamoyl group, and *n* represents zero or an integer 1 or 2, the substituents R^1 being the same or different when *n* represents 2, R^2 represents a hydrogen atom or a straight- or branched-chain alkyl group containing from 1 to 5 carbon atoms or an aryl group, and R^3 represents a hydrogen atom or a straight- or branched-chain alkyl group containing from 1 to 6 carbon atoms, optionally substituted by a phenyl group, or represents an aryl group optionally substituted by one or more substituents selected from halogen atoms, straight- or branched-chain alkyl and alkoxy groups contaning from 1 to 6 carbon atoms and hydroxy, trifluoromethyl and nitro groups], and pharmaceutically acceptable salts thereof.

2. Benzamide derivatives according to claim 1 wherein $(R^1)_n$ represents a straight- or branched-chain alkyl group containing from 1 to 6 carbon atoms, R^2 represents a hydrogen atom or a straight- or branched-chain alkyl group containing from 1 to 5 carbon atoms, and R^3 represents a hydrogen atom or a straight- or branched-chain alkyl group containing from 1 to 6 carbon atoms, or a phenyl or benzyl group, and pharmaceutically acceptable salts thereof.

3. Benzamide derivatives according to claim 1 wherein $(R^1)_n$ represents the methyl or ethyl group, R^2 represents a hydrogen atom or the methyl group, and R^3 represents a hydrogen atom or a straight- or branched-chain alkyl group containing from 1 to 3 carbon atoms, or a phenyl or benzyl group, and pharmaceutically acceptable salts thereof.

4. Benzamide derivatives according to claim 3 wherein R^3 represents the methyl or isopropyl group, and pharmaceutically acceptable salts thereof.

5. Benzamide derivatives according to any one of claims 1 to 4 wherein $(R^1)_n$ represents a substituent in the 5-position of the phenyl ring, and wherein the group $-CR^2=NOR^3$ is in the 3-position of the phenyl ring, and pharmaceutically acceptable salts thereof.

6. 5-Ethyl-2-hydroxy-3-[1-(hydroxyimino)ethyl]-*N*-(tetrazol-5-yl)benzamide.

7. 5-Ethyl-2-hydroxy-3-[1-(methoxyimino)ethyl]-*N*-(tetrazol-5-yl)benzamide.

8. 5-Ethyl-2-hydroxy-3-[1-(isopropoxyimino)ethyl]-*N*-(tetrazol-5-yl)benzamide.

9. 3-[1-(Benzyloxyimino)ethyl]-5-ethyl-2-hydroxy-*N*-(tetrazol-5-yl)benzamide.

10. 2-Hydroxy-3-[1-(hydroxyimino)ethyl]-5-methyl-*N*-(tetrazol-5-yl)benzamide.

11. 2-Hydroxy-3-[1-(methoxyimino)ethyl]-5-methyl-*N*-(tetrazol-5-yl)benzamide.

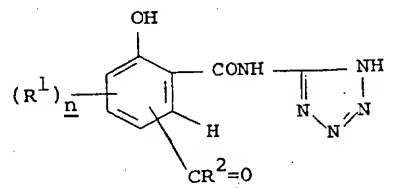
12. 2-Hydroxy-3-[1-(isopropoxyimino)ethyl]-5-methyl-*N*-(tetrazol-5-yl)benzamide.

13. 5-Ethyl-2-hydroxy-3-[1-(phenoxyimino)ethyl]-*N*-(tetrazol-5-yl)benzamide.

14. 2-Hydroxy-3-(methoxyimino)methyl-5-methyl-*N*-(tetrazol-5-yl)benzamide,

15. Pharmaceutically acceptable salts of a benzamide derivative claimed in any one of claims 6 to 14.

16. A process for the preparation of a benzamide derivative as claimed in claim 1 or a pharmaceutically acceptable salt thereof which comprises reacting a compound of the general formula:-



II

(wherein R^1, R^2 and *n* are as defined in claim 1) with a compound of the general formula:-

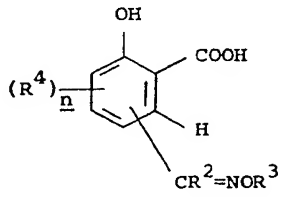
H_2NOR^3 III

(wherein R^3 is as defined in claim 1) in the form of a salt thereof, and optionally converting by known methods a benzamide derivative of the general formula specified in claim 1 thus obtained into a pharmaceutically acceptable salt.

17. A process according to claim 16 in which the hydrochloride of the compound of general formula III is used.

18. A process according to claim 16 or 17 in which the reaction is carried out in the presence of a base in a polar medium such as *N*-methylpyrrolidone and at a temperature of from 15° to 100°C.

19. A process for the preparation of a benzamide derivative of the general formula specified in claim 1 or a pharmaceutically acceptable salt thereof, except for such a compound wherein R^1 represents an alkylamino, amino or carboxy group which comprises reacting 5-aminotetrazole with a carboxylic acid of the general formula:-



IV

wherein R^4 represents a halogen atom or a straight- or branched-chain alkyl, alkoxy, alkylthio, alkylsulphonyl, or alkylsulphamoyl group, each such group containing from 1 to 6 carbon atoms, a dialkylsulphamoyl, dialkylamino, or dialkylcarbamoyl group (wherein the two alkyl groups may be the same or different and each contains from 1 to 4 carbon atoms), a straight- or branched-chain alkoxycarbonylamino, alkylcarbamoyl, or alkanoylamino group containing from 2 to 6 carbon atoms, or a hydroxy, nitro, trifluoromethyl, aryl, benzyloxycarbonylamino, sulphamoyl, tetrazol-5-yl or carbamoyl group, and *n* represents zero or an integer 1 or 2, the substituents R^4 being the same or different when *n* represents 2, and R^2 and R^3 are as defined in claim 1, and optionally converting by known methods a benzamide derivative of the general formula specified in claim 1 thus obtained into a phamaceutically acceptable salt.

20. A process according to claim 19 in which the reaction is carried out in the presence of a condensation agent such as dicyclohexylcarbodiimide in the presence of a solvent such a pyridine.

21. A process for the preparation of benzamide derivatives of the general formula specified in claim 1 and pharmaceutically acceptable salts thereof substantially as hereinbefore described with especial reference to Example 1.

22. A process for the preparation of benzamide derivatives of the general formula specified in claim 1 substantially as hereinbefore described in Example 2 or 3.

23. Benzamide derivatives of the general formula specified in claim 1 and pharmaceutically acceptable salts thereof when prepared by the process claimed in any one of claims 16 to 22.

24. Pharmaceutical compositions which comprise, as active ingredient, one or more benzamide derivatives as claimed in any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutical carrier or coating.

25. Pharmaceutical compositions according to claim 24 substantially as hereinbefore described.

26. Pharmaceutical compositions according to claim 24 substantially as hereinbefore described in Composition Example 1 or 2.

J.A. KEMP & CO.,
Chartered Patent Agents,
14, South Square,
Gray's Inn,
London, W.C.1.

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